J. Thomas Stocker, M.D.
B3098, X5-3480

Pathology of the Mediastinum

Required reading: Robbins; *Pathologic Basis of Disease*, Chapter 15 - Pages 690-3, Chapter 29 - Page 1289, Chapter 30 - Pages 1352-4

I. **Definition**

The mediastinum is the portion of the thoracic cavity located between the pleural cavities. It is delimited by the sternum anteriorly, the spine posteriorly, the diaphragm inferiorly and the thoracic inlet superiorly. It is divided arbitrarily into ***superior, anterior, middle and posterior*** compartments. The superior and anterior compartments are often considered together.

II. **Inflammatory Diseases of the Mediastinum**

CASE HISTORY

This 54 year old man complained of progressive dysphagia over a period of 6 months

A barium swallow displayed a narrowing in the distal esophagus which was surrounded by an irregular mass. A few days later, while eating, the patient experienced sudden chest pain and vomited fresh blood. The patient died a week later

A. *Acute Mediastinitis* - rare, usually resulting from esophageal perforation due to malignancy, foreign body or a diagnostic or therapeutic instrument. May lead to pneumothorax, pneumomediastinum or hydropneumothorax, and to the development of multiple abscesses.

B. *Chronic Sclerosing Mediastinitis* - fibrosis and granulomatous inflammation of the mediastinal soft tissues due to an infectious agent (usually *Histoplasma* or *Mycobacteria*) or, more frequently, without a specific etiology (idiopathic). Presents as ill-defined mass of inflammation and fibrosis which may compress vessels and airways in the hilar region. Granulomas with encased organisms may be seen in some cases.

III. **Pneumomediastinum**

CASE HISTORY

An infant was born prematurely at 28 weeks gestation with a birth weight of 1000 grams. He developed respiratory distress shortly after birth and was given synthetic surfactant through an endotracheal tube. Respiratory distress increased and he was placed on high frequency jet ventilation. Over the course of the next five days, two episodes of

pneumothorax occurred and were treated by placement of chest tubes. Chest x-ray displayed an interstitial pattern of disease. Respiratory distress progressed and the infant developed severe intraventricular hemorrhage and died.

A rarely occurring process seen most frequently in infants with the respiratory distress syndrome who are receiving mechanical ventilation that leads to interstitial pulmonary emphysema, pneumothorax, pneumopericardium and pneumomediastinum. May also be associated with esophageal perforation, closed chest trauma, protracted vomiting and Valsalva maneuvers (e.g. during parturition).

IV. **Mediastinal Hemorrhage**

Hemorrhage into the mediastinal tissues is usually seen in association with severe chest trauma (automobile accidents), but may also occur with rupture of a aortic aneurysm or perforation of a vein by faulty insertion of a central venous line.

V. **Most Common Mediastinal Masses (by Compartment)**

A. Superior/Anterior - bounded by the sternum anteriorly and the pericardium, aorta and brachiocephalic vessels posteriorly.

Case History

This 45 year old female presented with intermittent diplopia and ptosis and some muscular weakness in her limbs. She responded to anticholinesterase agents with transient improvement in strength (Tensilon test). A chest xray revealed an anterior mediastinal mass.

1. Thymoma - the thymus, while relatively large in infants, involutes during childhood and is often difficult to identify in adults.

   - a thymoma is a benign or malignant neoplasm of **thymic epithelium** that accounts for 12-20% of mediastinal tumors - second only to lymphoma. Seen most frequently in middle-aged patients (F:M=1.2:1). Of patients with thymoma, 30 - 50% will have ***Myasthenia Gravis*** (deficiency of acetylcholinesterase at the motor end-plate that produces fluctuating weakness of the external ocular muscles or of the general voluntary muscle system). Conversely, 15% of patients with MG have thymoma. Currently, survival rate for thymoma patients with or without MG is the same (about 67%).

   - also associated with other autoimmune diseases including hypogammaglobulinemia, erythroid hypoplasia, dermatomyositis, SLE, and rheumatoid arthritis.

- lesion consists of 5-15 cm in diameter masses that are largely solid, yellowish gray tissue and are separated into lobules by connective tissue septa. Cysts may be present. Microscopically, tumor is composed of mixture of neoplastic epithelial cells and non-neoplastic lymphocytes.

- variety of classifications based on behavior and histology. As listed in Robbins

Benign thymoma - 50% of tumors, cells resemble those of normal medulla, i.e. "*medullary thymoma*", are almost always benign. May see mixture of medullary-type epithelial cells with plumper type cortical cells along with few lymphocytes and Hassell corpuscles = "*mixed thymoma*". Excellent survival

Malignant thymoma

Type 1 - 20-25% of tumors - cytologically benign lesion that is *locally invasive* and may *metastasize widely* - composed of epithelial cells and lymphocytes - 50-90% survival depending on degree of invasion and metastases

Type 2 - 5% of tumors - cytologically malignant (anaplastic) epithelial cells "thymic carcinoma", metastasizes - esp. to lung. Poor survival

Treatment for these is by excision, and, when malignant, with additional radiation therapy and chemotherapy.

2. Thymic cyst- ***unilocular cyst*** **-** of developmental origin, small, more often in neck than mediastinum. Composed of thin transparent wall lined by flattened, cuboidal, columnar or squamous epithelium. Thymic tissue may be present in the wall.

- ***multilocular cyst*** - acquired process always accompanied by inflammation and fibrosis, may be incidental finding or produce symptoms. Walls of multilocular cysts lined by cuboidal, columnar of squamous epithelium that may be thin or highly reactive. Thought to arise from dilatation of medullary duct epithelium-derived structures. Similar changes may be seen in thymuses with Hodgkin's disease or seminoma (see below).

3. Thyroid Lesions -includes nodular hyperplasia of the thyroid gland that extends from the thyroid in the neck down into the superior mediastinum.

4. Germ Cell Tumors - account for 20% of mediastinal tumors and cysts

CASE HISTORY

This 38 year old male complained of mild dysphagia and respiratory distress. A chest xray displayed an anterior mediastinal mass which extended into the left hemithorax. Serum HCG - human chorionic gonadothrphin and AFP - alpha fetoprotein levels were NOT elevated

At autopsy a 15x12x8 cm mass was resected from the anterior mediastinum. Cut section showed solid and cystic areas with some cystic spaces containing hair and cheese-like material.

- probably arise from extragonadal germ cells - possibly of thymic origin. Must exclude metastasis of testicular or ovarian tumor origin. Associated with Klinefelter's syndrome (XXY and variants) and hematologic neoplasms (leukemia).

- types of tumors include seminoma (only in males), choriocarcinoma, mature cystic teratoma (the most common thymic germ cell tumor), embryonal carcinoma, endodermal sinus tumor and teratocarcinoma.

- serum human chorionic gonadotropin (HCG) and/or alpha-fetoprotein (AFP) are elevated in malignant nonseminomatous germ cell tumors.

5. Malignant Lymphoma - present in mediastinum as a primary disease or as a manifestation of a disseminated process.

   - most common primary neoplasm of middle mediastinum (see below)

   - types include *Hodgkins disease* (most frequently nodular sclerosing type), *lymphoblastic convoluted cell lymphoma* (especially in males), *large cell lymphoma* (females with superior vena cava syndrome).

6. Parathyroid Adenoma - accounts for 7% of all parathyroid adenomas

7. Paraganglioma - usually nonfunctioning, but may produce hypertension.

   - occasionally part of *Carney's triad* (gastric stromal tumor, pulmonary hamartomas, extra-adrenal paragangliomas)

8. Lymphangioma - most commonly seen in children, also called cystic hygroma

CASE HISTORY

A 13 year old male complained of shortness of breath on exertion and a mild progressive discomfort in his chest. A chest xray showed an anterior mediastinal mass which seemed to extend into and surround the structures in the pulmonary hilum. HCG and AFP were not elevated. At surgery a multicystic mass was resected from the anterior mediastinum and from around the hilar structures. The lesion recurred one year after surgery and eventually surrounded the pulmonary hilar structures and large vessels of the middle mediastinum causing the death of the boy.

9. Hemangioma - of cavernous type (large dilated vessels lined by flattened endothelium) in adults, or hemangioendotheliomatous type (small vascular channels lined by plump endothelial cells) in children.

10. Lipoma - benign tumor of adipose tissue, most frequent benign mesenchymal neoplasm in the mediastinum. Often large and located just above the diaphragm.

11. Metastatic Carcinoma - most common type of mediastinal mass in older patients (from bronchogenic carcinoma). Small cell carcinoma of the lung may present with massive enlarged mediastinal lymph nodes in the presence of a small primary pulmonary lesion.

12. Aneurysms

B. **Middle** - extends from the posterior limit of the anterior compartment to the posterior pericardial line and contains the 1) pericardium, 2) heart and all vessels entering or leaving it, 3) trachea and main bronchi, 4) paratracheal and tracheobronchial lymph nodes, 5) phrenic nerves, and, 6) upper portion of vagus nerve

1. Pericardial Cyst - results from failure of fusion of the lacunar cavities that form the pericardium. Usually located at the right cardiophrenic angle. May become infected.

2. Bronchogenic Cyst

CASE HISTORY

A 23 year old army recruit was noted on routine chest xray to have a circular "shadow" superimposed on his heart. He denied chest pain, fever and shortness of breath. At surgery, a 9 cm in diameter cyst attached to the pericardium was removed from the middle mediastinum. The cyst was filled with clear fluid.

- formed from pinched-off cells of developing foregut, one extension of which forms the lungs. These clusters of cells develop into a cyst usually located in the region of the carina. The cyst wall is lined by respiratory epithelium and contains submucosal glands, smooth muscle, and cartilage plates.

3. Malignant Lymphoma - most common primary neoplasm of middle mediastinum.

4. Aneurysms

C. **Posterior** - lies posterior to the pericardium and anterior to the spine and contains the 1) descending thoracic aorta, 2) esophagus, 3) thoracic duct, 4) lower portion of the vagus nerve, and 5) posterior group of mediastinal lymph nodes

1. Neurogenic Tumors - the most common primary mediastinal tumor, accounting for 20% of tumors. Are tumors of *sympathetic nervous system - SNS* (seen in children under 10 years of age) or *peripheral nerve sheaths - PNS* (seen in patients over 20 years of age

a. Neurilemoma - benign, slowly growing neoplasm of Schwann cells that arises in a nerve. Often oval and well circumscribed. Composed of interwoven fascicles of spindle cells with elongated nuclei, eosinophilic cytoplasm and indistinct cytoplasmic borders (Antonio type A pattern) and spindle or oval cells with indistinct cytoplasm in a loose, vacuolated background (Antonio type B pattern).

b. Neurofibroma - a tumor representing a combined proliferation of all the elements of a peripheral nerve including axons, Schwann cells, fibroblasts and perineural cells. May be solitary or multiple. When multiple is diagnostic of neurofibromatosis.

c. Ganglioneuroma - SNS tumor seen in older children and adults. Smooth well encapsulated mass that is soft and yellowish-grey. Contains a mixture of ganglion cells, Schwann's cells or satellite cells and mature lymphocytes. May represent "matured" ganglioneuroblastoma.

d. Ganglioneuroblastoma - SNS tumor in children that is composed of, 1) immature , multinucleated ganglion cells in a neurofibrillary matrix or, 2) mature ganglion cells along with well-defined areas of neuroblastoma.

e. Neuroblastoma

CASE HISTORY

A 3 year old girl presented with a two week history of watery diarrhea. Urinary catecholamines - VMA and HVA - were elevated

Chest xray and CT displayed a large posterior mediastinal mass

- SNS tumor, the most common solid tumor of children (after CNS tumors) that is usually found in the adrenal gland in children under two years of age. Calcification may be identified by imaging studies. Extraadrenal site has better prognosis. Consists of large, soft, focally hemorrhagic and necrotic tissue. Composed of “small, round, blue” cells in a pink neurofibrillary matrix. Also see calcification, necrosis, Homer-Wright rosettes, and, in some cases, larger cells resembling poorly differentiated ganglion cells.

f. Malignant Schwannoma

g. Paraganglioma - (see under anterior mediastinum above)

2. Gastroenteric Cyst - duplication of segment of foregut. May resemble esophagus or stomach. Often filled with fluid, but may retain fistulas attachment to esophagus or bronchus. May lie within the wall of the esophagus. Frequently associated with vertebral anomalies (e.g., butterfly vertebrae)

3. Aneurysms